

Serum Uric Acid and Risk for Cardiovascular Disease and Death: The Framingham Heart Study

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Background: Hyperuricemia is associated with risk for cardiovascular disease and death. However, the role of uric acid independent of established risk factors is uncertain.

Objective: To examine the relation of serum uric acid level to incident coronary heart disease, death from cardiovascular disease, and death from all causes.

Design: Community-based, prospective observational study.

Setting: Framingham, Massachusetts.

Patients: 6763 Framingham Heart Study participants (mean age, 47 years).

Measurements: Serum uric acid level at baseline (1971 to 1976); event rates per 1000 person-years by sex-specific uric acid quintile.

Results: During 117 376 person-years of follow-up, 617 coronary heart disease events, 429 cardiovascular disease deaths, and 1460 deaths from all causes occurred. In men, after adjustment for age, elevated serum uric acid level was not associated with increased risk for an adverse outcome. In women, after adjustment for age, uric acid level was predictive of coronary heart disease ($P = 0.002$), death from cardiovascular disease ($P = 0.009$), and death from all causes ($P = 0.03$). After additional adjustment for cardiovascular disease risk factors, uric acid level was no longer associated with coronary heart disease, death from cardiovascular disease, or death from all causes. In a stepwise Cox model, diuretic use was identified as the covariate responsible for rendering serum uric acid a statistically nonsignificant predictor of outcomes.

Conclusions: These findings indicate that uric acid does not have a causal role in the development of coronary heart disease, death from cardiovascular disease, or death from all causes. Any apparent association with these outcomes is probably due to the association of uric acid level with other risk factors.

The association of serum uric acid with cardiovascular disease has been appreciated for nearly half a century (1). Several prospective studies have shown an association between baseline hyperuricemia and incident coronary heart disease, cardiovascular disease, and death (2–10). Despite the strength of these associations, uric acid has not been established as a causal risk factor for cardiovascular disease. Instead, uric acid seems inextricably linked to hypertension, dyslipidemia, and disordered glucose metabolism, which play a causal role in the pathogenesis of cardiovascular disease. As such, uric acid may be merely a marker of risk for cardiovascular disease.

Several recent reports, however, have attempted to dispel this notion (3, 9, 11–14). Using data from the First National Health and Nutrition Examination Study (NHANES I), Freedman and colleagues (3) demonstrated that each 60- $\mu\text{mol/L}$ increment in uric acid level was associated with a 48% increase in risk for incident ischemic heart disease among women. Furthermore, a growing body of laboratory and clinical evidence suggests that uric acid plays a role in platelet adhesiveness (15–17), formation of free radicals (18), and oxidative stress (19, 20).

As a result of this growing controversy, we revisited this question in the Framingham Heart Study sample. Longer and more contemporary follow-up and more outcome events allowed us to expand on a previous Framingham report (2). In this paper, we describe the relation of baseline serum uric acid level to 1) incident coronary heart disease events (death from coronary heart disease, recognized myocardial infarction, and coronary insufficiency), 2) death from cardiovascular disease, and 3) death from all causes. Because previous studies (2, 3, 7, 21) have suggested that uric acid is more strongly associated with adverse events in women than in men, we chose *a priori* to perform sex-specific analyses.

Methods

Study Sample

The selection criteria and study design of the Framingham Heart Study and the Framingham Off-

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See editorial comment on pp 62-63.

Table 1. Baseline Clinical Characteristics*

Characteristic	Men (n = 3075)	Women (n = 3688)
Age, y	46 ± 15	48 ± 16
Serum uric acid level, $\mu\text{mol/L}$	379 ± 76	285 ± 69
Body mass index, kg/m^2	26.7 ± 3.6	24.8 ± 4.7
Systolic blood pressure, mm Hg	130 ± 17	126 ± 21
Diastolic blood pressure, mm Hg	82 ± 11	77 ± 10
Hypertension, %	32.6	28.7
Antihypertensive use, %	8.0	11.6
Diuretic use, %	4.9	9.7
Left ventricular hypertrophy, %	0.7	0.4
Diabetes, %	3.9	2.5
Total serum cholesterol level, mmol/L	5.35 ± 1.02	5.40 ± 1.17
Weekly alcohol use, oz	5.5 ± 6.4	2.2 ± 3.1
Smoker, %	45.9	37.8
Postmenopausal, %	—	49.4

* Values with plus/minus sign are the mean ± SD.

spring Study have been described elsewhere (22, 23). Original participants of the Framingham Heart Study who took part in the 13th biennial examination (1972 to 1976) and adult participants in the first examination of the Framingham Offspring Study (1971 to 1975) were eligible for this investigation ($n = 7940$). Blood samples for uric acid measurement were obtained in 7650 (96.3%) persons. Participants were excluded ($n = 887$) for the following reasons: use of more than 2 g of salicylates per day ($n = 17$), missing covariate or follow-up data ($n = 117$), and prevalent cardiovascular disease ($n = 753$). The remaining 6763 participants were followed prospectively until 1994.

Baseline Measurements and Definitions

Medical histories and physical examinations were performed for each participant at every clinic visit. Systolic and diastolic blood pressure were measured twice in the left arm of seated participants by using a mercury-column sphygmomanometer positioned near eye level. The average of the two readings was used for each blood pressure variable. The diagnosis of hypertension was based on a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or the current use of antihypertensive drugs (24).

Height and weight were measured at each examination, and body mass index was calculated as the weight in kilograms divided by the square of the height in meters. Participants who reported smoking at least one cigarette per day during the year before the examination were classified as current smokers. Alcohol use was ascertained by self-report and was categorized as ounces of ethanol consumed per week. Menopause was defined as the absence of menses for 1 year or more.

Diabetes was defined on the basis of a nonfasting blood glucose level of 11.1 mmol/L (200 mg/dL) or greater, a fasting blood glucose level of 7.8 mmol/L

(140 mg/dL) or greater, or the use of insulin or an oral hypoglycemic agent.

Serum uric acid levels were measured with an autoanalyzer that used a phosphotungstic acid reagent (25). Cholesterol levels were determined according to the Abell-Kendall method (26).

Outcome Events

The primary outcome measures were incident coronary heart disease events, death from cardiovascular disease (coronary heart disease, congestive heart failure, stroke, or other cardiovascular disease), and death from all causes. Coronary heart disease events included the following: death from coronary heart disease (available information suggested coronary heart disease as the probable cause), recognized myocardial infarction (serial electrocardiographic changes leading to development of new pathologic Q waves, characteristic increase and decrease in serum myocardial markers with a suggestive clinical history, or evidence at necropsy of new or recent infarction), and coronary insufficiency (prolonged ischemic chest discomfort associated with transient repolarization abnormality, without criteria for myocardial infarction). Events that were more equivocal, such as unrecognized myocardial infarction and angina pectoris, were not included as coronary heart disease events for this analysis. A panel of three physicians determined the outcome events according to previously published criteria (27) after reviewing Framingham Heart Study and outside hospital and physician records.

Statistical Analysis

Separate analyses were performed for men and women. All participants were divided according to sex-specific uric acid quintiles. Crude event rates were calculated for each quintile. Cox proportional hazards regression models (28) were used to examine the relations of uric acid quintiles (with quintile 1 as the reference category) and the relation of uric

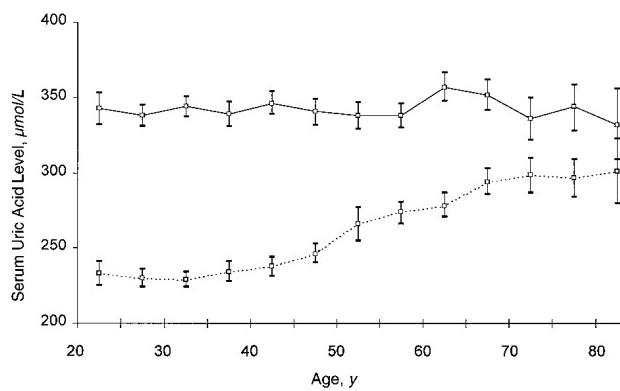


Figure. Mean serum uric acid level by sex and 5-year age group. Solid line represents men; dashed line represents women; squares represent values at midpoint of 5-year age group; and vertical bars represent 95% CIs.

Table 2. Relations of Serum Uric Acid Level to Coronary Heart Disease, Death from Cardiovascular Disease, and Death from All Causes

Uric Acid Quintile	Events, n	Rate per 1000 Person-Years	Hazard Ratio (95% CI)		
			Unadjusted	Adjusted for Age	Fully Adjusted*
Coronary heart disease					
Men					
Quintile 1 (<280 μmol/L)	86	8.7	1	1	1
Quintile 2 (280–315 μmol/L)	90	8.8	1.01 (0.75–1.36)	1.08 (0.80–1.45)	1.13 (0.84–1.53)
Quintile 3 (316–351 μmol/L)	63	6.1	0.70 (0.51–0.97)	0.80 (0.57–1.10)	0.85 (0.61–1.19)
Quintile 4 (352–399 μmol/L)	83	7.9	0.90 (0.67–1.22)	0.94 (0.70–1.27)	0.94 (0.69–1.28)
Quintile 5 (≥400 μmol/L)	72	7.2	0.83 (0.60–1.13)	0.77 (0.56–1.05)	0.73 (0.52–1.02)
P for trend			0.15	0.06	0.03
Women					
Quintile 1 (<196 μmol/L)	25	1.9	1	1	1
Quintile 2 (196–226 μmol/L)	24	1.8	0.99 (0.57–1.74)	0.97 (0.55–1.69)	0.92 (0.52–1.61)
Quintile 3 (227–262 μmol/L)	36	2.7	1.47 (0.89–2.46)	1.29 (0.78–2.15)	1.18 (0.71–1.97)
Quintile 4 (263–310 μmol/L)	50	4.0	2.17 (1.35–3.52)	1.20 (0.74–1.95)	1.05 (0.64–1.71)
Quintile 5 (≥311 μmol/L)	88	7.5	4.11 (2.64–6.42)	1.80 (1.15–2.84)	1.25 (0.78–2.02)
P for trend			<0.001	0.002	>0.2
Death from cardiovascular disease					
Men					
Quintile 1 (<280 μmol/L)	47	4.6	1	1	1
Quintile 2 (280–315 μmol/L)	52	4.8	1.07 (0.72–1.59)	1.18 (0.79–1.75)	1.21 (0.80–1.81)
Quintile 3 (316–351 μmol/L)	34	3.2	0.70 (0.45–1.09)	0.84 (0.54–1.31)	0.90 (0.58–1.42)
Quintile 4 (352–399 μmol/L)	49	4.5	0.98 (0.66–1.46)	1.04 (0.70–1.56)	0.99 (0.65–1.49)
Quintile 5 (≥400 μmol/L)	50	4.9	1.08 (0.72–1.60)	1.02 (0.69–1.52)	0.92 (0.61–1.40)
P for trend			>0.2	>0.2	>0.2
Women					
Quintile 1 (<196 μmol/L)	17	1.3	1	1	1
Quintile 2 (196–226 μmol/L)	23	1.8	1.39 (0.74–2.61)	1.29 (0.69–2.42)	1.24 (0.66–2.34)
Quintile 3 (227–262 μmol/L)	28	2.1	1.68 (0.92–3.07)	1.46 (0.80–2.66)	1.38 (0.75–2.54)
Quintile 4 (263–310 μmol/L)	45	3.6	2.85 (1.63–4.98)	1.37 (0.79–2.41)	1.26 (0.72–2.22)
Quintile 5 (≥311 μmol/L)	84	7.0	5.69 (3.38–9.58)	1.93 (1.14–3.26)	1.46 (0.84–2.53)
P for trend			<0.001	0.009	>0.2
Death from all causes					
Men					
Quintile 1 (<280 μmol/L)	154	15.0	1	1	1
Quintile 2 (280–315 μmol/L)	170	15.8	1.07 (0.86–1.33)	1.17 (0.94–1.46)	1.24 (0.99–1.54)
Quintile 3 (316–351 μmol/L)	105	9.9	0.66 (0.51–0.85)	0.79 (0.61–1.01)	0.85 (0.66–1.10)
Quintile 4 (352–399 μmol/L)	143	13.1	0.87 (0.70–1.10)	0.93 (0.74–1.17)	0.96 (0.76–1.21)
Quintile 5 (≥400 μmol/L)	157	15.3	1.04 (0.83–1.29)	0.98 (0.78–1.22)	0.98 (0.78–1.24)
P for trend			>0.2	>0.2	>0.2
Women					
Quintile 1 (<196 μmol/L)	85	6.3	1	1	1
Quintile 2 (196–226 μmol/L)	99	7.5	1.19 (0.89–1.60)	1.11 (0.83–1.48)	1.07 (0.80–1.43)
Quintile 3 (227–262 μmol/L)	111	8.3	1.31 (0.99–1.74)	1.15 (0.87–1.53)	1.11 (0.84–1.48)
Quintile 4 (263–310 μmol/L)	174	13.8	2.22 (1.71–2.88)	1.13 (0.87–1.47)	1.09 (0.84–1.42)
Quintile 5 (≥311 μmol/L)	262	21.8	3.63 (2.84–4.63)	1.32 (1.03–1.70)	1.16 (0.89–1.51)
P for trend			<0.001	0.03	>0.2

* Adjusted for age, body mass index, systolic blood pressure, use of antihypertensive agents, use of diuretics, diabetes, total cholesterol level, smoking status, alcohol intake, left ventricular hypertrophy, and menopausal status.

acid level as a continuous variable to incidence of coronary heart disease events, cardiovascular disease mortality rates, and all-cause mortality rates. For comparative purposes, hazard ratios were calculated without adjustment. For inferential purposes, hazard ratios were calculated with adjustment for age only and also with adjustment for age and other clinical variables associated with uric acid level or atherosclerotic events: body mass index (kg/m^2), diabetes (yes/no), systolic blood pressure (mm Hg), current diuretic use (yes/no), use of antihypertensive medications other than diuretics (yes/no), left ventricular hypertrophy shown on electrocardiography (yes/no), total cholesterol level (mmol/L), smoking status (yes/no), alcohol use (ounces consumed per week), and menopausal status in women (yes/no). Post hoc subgroup analyses were done to determine any possible relations between quintiles

of uric acid and the outcome events in participants stratified according to diuretic use and hypertension status.

All analyses were performed on a Sun Ultra-SPARC computer (Sun Microsystems, Mountain View, California) using SAS software (SAS Institute, Cary, North Carolina) (29). A two-sided P value less than 0.05 was the criterion for statistical significance.

Results

Participant Characteristics

Table 1 shows the baseline clinical characteristics for men and women. The mean uric acid level was 379 μmol/L in men (range, 119 to 738 μmol/L) and 285 μmol/L in women (range, 24 to 696 μmol/L).

Table 3. *P* Values for Uric Acid Quintile Trend among Women in Stepwise Cox Proportional Hazards Analyses

Step	Coronary Heart Disease		Death from Cardiovascular Disease		Death from All Causes	
	Covariate	P Value	Covariate	P Value	Covariate	P Value
0*		0.002		0.009		0.026
1	Systolic blood pressure	0.008	Systolic blood pressure	0.013	Smoking	0.043
2	Cholesterol level	0.031	Diabetes	0.016	Systolic blood pressure	0.064
3	Smoking	0.044	Smoking	0.018	Diabetes	0.081
4	Diabetes	0.046	Diuretic treatment	0.072	Diuretic treatment	>0.2
5	Diuretic treatment	0.18	Left ventricular hypertrophy	0.090	Hypertension treatment†	>0.2
6	Body mass index	0.2	Cholesterol level	0.13	Left ventricular hypertrophy	>0.2
7	Left ventricular hypertrophy	>0.2	Hypertension treatment†	0.17	Cholesterol level	>0.2

* All models include age and uric acid quintile.

† Other than treatment with diuretics.

The effect of age on mean serum uric acid level is illustrated in the **Figure**. In men, uric acid levels changed minimally with age. In women, mean serum uric acid levels gradually increased from the fourth to the seventh decades of life. Furthermore, among women 30 to 54 years of age, the mean serum uric acid level was 5 to 13 $\mu\text{mol/L}$ greater in those who were postmenopausal (data not shown).

Uric Acid Level and Outcome Events

There were 117 376 person-years of follow-up. In men, 394 coronary heart disease events, 232 deaths due to cardiovascular disease, and 729 deaths from all causes occurred. As a continuous variable, baseline uric acid level was not associated with increased risk for any end point in men. In fully adjusted Cox models, for every 60- $\mu\text{mol/L}$ increase in serum uric acid level, hazard ratios were as follows: 0.91 (95% CI, 0.83 to 0.99) for coronary heart disease, 0.95 (CI, 0.86 to 1.06) for death from cardiovascular disease, and 0.97 (CI, 0.91 to 1.03) for death from all causes. In men, baseline quintile of serum uric acid level was also not associated with increased risk for any outcome measure. Uric acid level was inversely related to coronary heart disease in the full multivariable adjusted model (**Table 2**).

In women, 223 coronary heart disease events, 197 deaths from cardiovascular disease, and 731 deaths from all causes occurred. From quintile 1 to quintile 5, crude rates increased more than threefold for coronary heart disease (from 1.9 to 7.5 per 1000 person-years), death from cardiovascular disease (from 1.3 to 7.0 per 1000 person-years) and death from all causes (from 6.3 to 21.8 per 1000 person-years) (**Table 2**). In unadjusted Cox models in which quintile 1 was the reference category, risk significantly increased with increasing uric acid quintile for all three outcome measures ($P < 0.001$ for trend). This trend diminished after adjustment for age but remained significant for coronary heart disease ($P = 0.002$), death from cardiovascular disease ($P = 0.009$), and death from all causes ($P = 0.03$). In fully adjusted Cox models, baseline uric acid

level was no longer associated with increased risk for coronary heart disease ($P > 0.2$ for trend), death from cardiovascular disease ($P = 0.23$), or death from all causes ($P > 0.2$). Similar relations were found when baseline uric acid level was assessed as a continuous variable. In the fully adjusted models, hazard ratios for every 60- $\mu\text{mol/L}$ increase in serum uric acid level were as follows: 1.05 (CI, 0.94 to 1.17) for coronary heart disease, 1.01 (CI, 0.90 to 1.13) for death from cardiovascular disease, and 1.03 (CI, 0.97 to 1.09) for death from all causes.

To identify the covariates largely responsible for the declining association between baseline uric acid level and the outcome measures among women, we assessed the *P* value for quintile trend after each covariate was added to the stepwise Cox models (**Table 3**). Established risk factors, such as blood pressure, smoking, total cholesterol level, diabetes, and diuretic use were responsible for the declining quintile trend with each end point.

Subgroup Analyses

Approximately one third of men and 30% of women were hypertensive, and 5% of men and 10% of women were receiving diuretics. Among these subgroups, baseline uric acid level was not associated with subsequent coronary heart disease, death from cardiovascular disease, or death from all causes (**Table 4**).

Discussion

In this prospective community-based study of 6763 men and women, serum uric acid level was not associated with increased risk for coronary heart disease, death from cardiovascular disease, or death from all causes after adjustment for risk factors and potential confounders. Although our findings are negative and contrary to those recently reported (3, 6, 9, 11–13), they provide insight into the association between uric acid and cardiovascular disease. We also offer an explanation for the discrepancy

between our results and findings of other studies that had suggested a positive association between uric acid and cardiovascular outcomes.

Prospective studies examining the relation of serum uric acid level to incident cardiovascular events have differed substantially in study design. These differences probably explain the disparate results in the literature. Some authors combined the results for men and women after adjustment for sex (8, 9, 12, 13), whereas others performed sex-specific analyses (2–4, 7). We believed a priori that sex-specific analyses were required because at all ages, the serum uric acid level is higher in men than in women (**Figure 1**). In addition, previous studies have suggested that uric acid levels are more strongly associated with adverse events in women than in men (2, 3, 7, 21). Uric acid is also associated with diabetes and glucose intolerance, risk factors that confer greater relative risk for cardiovascular disease in women (30–32).

The management of prevalent cardiovascular disease at the inception of each of these previous studies has also varied considerably. Most studies did not exclude persons with cardiovascular disease at baseline (4, 8, 9, 12, 13) or excluded only those with prevalent coronary heart disease but not other manifestations of cardiovascular disease (2, 3, 5). With such an approach, it is inherently difficult to determine whether incident cardiovascular disease events are related to the preexisting disease or to the uric acid level. Because our goal was to determine the relation of baseline serum uric acid level to initial incident cardiovascular events, we considered it necessary to exclude participants with prevalent cardiovascular disease at baseline.

The degree of adjustment for possible confounding variables has also differed substantially among

the observational studies to date. Although most authors controlled for age, relative weight, blood pressure, and serum cholesterol level, many of the same investigators did not adjust for diabetes (2, 4), antihypertensive therapy (4–6), or diuretic use (4, 6, 7). A recent report (3) seems to have accounted for diabetes by excluding diabetic patients from the longitudinal analyses, but diabetes was identified solely by self-report. A misclassification bias may be responsible for residual confounding because about half of persons with type 2 diabetes are unaware of their diagnosis (33).

Among men in our study, elevated serum uric acid level was associated with decreased incidence of coronary heart disease. We found no association between baseline serum uric acid level and death from cardiovascular disease or death from all causes. The unexpected inverse relation between uric acid level and coronary heart disease is difficult to explain and may be the result of chance associated with the testing of multiple hypotheses. Another possibility is that the finding may reflect prolonged event-free survival of persons of high socioeconomic status, in whom hyperuricemia and gout are more common (34, 35). Unfortunately, the information necessary to adjust for socioeconomic status in the current study was unavailable.

With the exception of two investigations (6, 11), most previous prospective studies have not found a positive association between serum uric acid level and risk for cardiovascular disease in men. Differences in participant characteristics or statistical techniques may explain the discrepancy between the results in an Augsburg, Germany, cohort and our findings. Mean total cholesterol levels and mean systolic and diastolic blood pressures in the German cohort (36) were greater than those in Framingham

Table 4. Risk for Outcome Events in the Subgroup with Hypertension and the Subgroup Receiving Diuretics*

Subgroup	Participants at Risk	Coronary Heart Disease		Death from Cardiovascular Disease		Death from All Causes								
		Events	Hazard Ratio (95% CI)	Events	Hazard Ratio (95% CI)	Events	Hazard Ratio (95% CI)							
n														
Hypertension														
Men														
No	2074	210	0.90 (0.81–1.00)	105	1.05 (0.91–1.21)	369	0.95 (0.88–1.02)							
Yes	1001	184	0.94 (0.85–1.05)	127	0.92 (0.81–1.04)	360	0.99 (0.92–1.07)							
Women														
No	2627	81	1.05 (0.88–1.24)	57	1.00 (0.82–1.23)	305	1.06 (0.97–1.15)							
Yes	1060	142	1.07 (0.93–1.22)	140	1.10 (0.96–1.27)	426	1.02 (0.95–1.10)							
Diuretic treatment														
Men														
No	2923	361	0.92 (0.79–1.07)	209	0.95 (0.86–1.04)	659	0.97 (0.92–1.09)							
Yes	152	33	0.87 (0.76–1.12)	23	1.07 (0.78–1.48)	70	0.94 (0.79–1.13)							
Women														
No	3329	162	1.00 (0.88–1.12)	140	1.04 (0.92–1.18)	569	1.02 (0.96–1.09)							
Yes	358	61	1.27 (0.97–1.66)	57	1.17 (0.90–1.52)	162	1.03 (0.89–1.19)							

* Hazard ratios are given for uric acid quintile trend. Analyses adjusted for age, body mass index, systolic blood pressure, use of antihypertensive agents (in the diuretic subgroup), use of diuretics (in the hypertension subgroup), diabetes, total cholesterol level, smoking status, alcohol intake, left ventricular hypertrophy, and menopausal status (among women).

men of similar age. Furthermore, the German study did not adjust for three relevant confounders: altered glucose metabolism, relative weight, and diuretic use. In the Honolulu Heart Study (6), elevated uric acid level was associated with incident angina in men. Again, the investigators did not adjust for diuretic use. In addition, when the coronary heart disease outcome was analyzed by using definite coronary heart disease instead of the more equivocal outcome, uric acid level was no longer associated with coronary events.

Among women, we found a strong and graded association between baseline uric acid level and increased risk for coronary heart disease, death from cardiovascular disease, and death from all causes. These findings are similar to those seen in previous studies (2–5, 7). This risk was reduced substantially after adjustment for age, and it was eliminated completely in the multivariate model. In a subsequent stepwise Cox analysis, we identified the covariates responsible for the loss of uric acid's statistical significance: blood pressure, total cholesterol level, smoking, diabetes, and, in particular, diuretic therapy. In addition to inducing hyperuricemia, diuretic therapy frequently worsens lipid levels and glucose tolerance (37–40). Furthermore, diuretic therapy is probably a marker for more severe hypertension.

Mechanisms by which uric acid may be associated with atherosclerotic disease remain uncertain. A large body of evidence links uric acid with the metabolic syndrome of insulin resistance, obesity, hypertension, and dyslipidemia (41). Several studies have shown an inverse relation between uric acid excretion and insulin level (42, 43). Insulin has also been found to promote the tubular reabsorption of sodium (44). Cappuccio and colleagues (45) reported an association of hyperuricemia with increased renal tubular sodium reabsorption, thus providing a link with hyperuricemia, hypertension, and hyperinsulinemia.

Uric acid may also be an indicator for increased oxidative stress. Xanthine oxidase, a critical enzyme in the degradation of purines to uric acid, has been shown to be an important source of superoxide free radicals (46). The activity of xanthine oxidase increases during ischemia and intensifies during reperfusion in coronary endothelial cells (47). In animals, allopurinol limits infarction size (48) and enhances recovery of stunned myocardium (49), perhaps by limiting the generation of toxic free radicals. Clinically, hyperuricemia occurs during interruption of limb arterial flow (50), after coronary angioplasty (51), during coronary artery bypass surgery (52), and in other hypoxic states (19, 20, 47, 53–56).

Several potential limitations of the present study should be considered. First, most participants were white. The results may not apply to nonwhite, non-

European populations. Second, data on several important clinical characteristics were unavailable. Renal function and insulin resistance were not measured at the time of data collection. Finally, the analyses in the diuretic and antihypertensive subgroups were limited by the number of participants in each category. The results of these subgroup analyses should be viewed as hypothesis-generating only.

Despite these limitations, however, we believe that our study adds to the current literature. This report is more contemporary than a previous Framingham Heart Study article (2) and included far more outcome events and subgroup analyses. Furthermore, the 23 years of follow-up in the current investigation is the longest to date. As a result, the number of outcome events is greater than in previously reported observational studies. We also adjusted for several relevant risk factors and potential confounders not available in many other cohort studies. Finally, each outcome event in this investigation was determined by a panel of three physicians according to a standardized protocol; other studies, in contrast, relied on death certificate or hospital record coding.

Our findings from a community-based prospective study of 6763 adult men and women suggest that an elevated serum uric acid level is not causally associated with increased risk for coronary heart disease, death from cardiovascular disease, or death from all causes. Associations reported in age-adjusted models are probably due to confounding, particularly by diuretic use. From a clinical perspective, serum uric acid level should not be used as an indicator of risk for cardiovascular disease; established risk factors should be used to stratify risk (57).

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References

1. Gertler MM, Garn SM, Levine SA. Serum uric acid in relation to age and physique in health and in coronary heart disease. Ann Intern Med. 1951;34: 1421–31.
2. Brand FN, McGee DL, Kannel WB, Stokes J 3d, Castelli WP. Hyperuricemia as a risk factor of coronary heart disease: the Framingham study. Am J Epidemiol. 1985;121:11–8.

- 3. Freedman DS, Williamson DF, Gunter EW, Byers T.** Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow-Up Study. *Am J Epidemiol.* 1995;141:637-44.
- 4. Levine W, Dyer AR, Shekelle RB, Schoenberger JA, Stamler J.** Serum uric acid and 11.5-year mortality of middle-aged women: findings of the Chicago Heart Association Detection Project in Industry. *J Clin Epidemiol.* 1989;42:257-67.
- 5. Bengtsson C, Lapidus L, Stendahl C, Waldenstrom J.** Hyperuricaemia and risk of cardiovascular disease and overall death. A 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. *Acta Med Scand.* 1988;224:549-55.
- 6. Yano K, Reed DM, McGee DL.** Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to biologic and lifestyle characteristics. *Am J Epidemiol.* 1984;119:653-66.
- 7. Reunanan A, Takkenen H, Knekt P, Aromaa A.** Hyperuricemia as a risk factor for cardiovascular mortality. *Acta Med Scand Suppl.* 1982;668:49-59.
- 8. Mortality findings for stepped-care and referred-care participants in the Hypertension Detection and Follow-up Program, stratified by other risk factors. The Hypertension and Follow-up Program Cooperative Research Group.** *Prev Med.* 1985;14:312-35.
- 9. Lehto S, Niskanen L, Ronnemaa T, Laakso M.** Serum uric acid is a strong predictor of stroke in patients with non-insulin-dependent diabetes mellitus. *Stroke.* 1998;29:635-9.
- 10. Wannamethee SG, Shaper AG, Whincup PH.** Serum urate and the risk of major coronary heart disease events. *Heart.* 1997;78:147-53.
- 11. Liese AD, Hense HW, Lowel H, Doring A, Keil U.** Association of serum uric acid with incident myocardial infarction, all cause and CVD mortality in the MONICA Augsburg cohort [Abstract]. *Circulation.* 1998;97:822.
- 12. Alderman MH, Kivlighn S, Beauchard L, Cohen H, Madhavan S.** Increased serum uric acid associated with increased cardiovascular disease in treated hypertensive patients [Abstract]. *J Hypertens.* 1998;16:5.
- 13. Alderman MH, Cohen H, Kivlighn S, Madhavan S.** Does treatment-mediated increase in uric acid reduce the cardioprotective effect of diuretics in hypertensive patients? [Abstract] *Am J Hypertens.* 1998;11:16.
- 14. Ward HJ.** Uric acid as an independent risk factor in the treatment of hypertension. *Lancet.* 1998;352:670-1.
- 15. Emmerson BT.** Atherosclerosis and urate metabolism. *Aust N Z J Med.* 1979; 9:451-4.
- 16. Newland H.** Hyperuricemia in coronary, cerebral and peripheral arterial disease: an explanation. *Med Hypotheses.* 1975;1:152-5.
- 17. Ginsberg MH, Kozin F, O'Malley M, McCarty DJ.** Release of platelet constituents by monosodium urate crystals. *J Clin Invest.* 1977;60:999-1007.
- 18. Vasquez-Vivar J, Santos AM, Junqueira VB, Augusto O.** Peroxynitrite-mediated formation of free radicals in human plasma: EPR detection of ascorbyl, albumin-thiyl and uric acid-derived free radicals. *Biochem J.* 1996;314: 869-76.
- 19. Anker SD, Leyva F, Poole-Wilson PA, Kox WJ, Stevenson JC, Coats AJ.** Relation between serum uric acid and lower limb blood flow in patients with chronic heart failure. *Heart.* 1997;78:39-43.
- 20. Leyva F, Anker S, Swan JW, Godsland IF, Wingrove CS, Chua TP, et al.** Serum uric acid as an index of impaired oxidative metabolism in chronic heart failure. *Eur Heart J.* 1997;18:858-65.
- 21. Persky VW, Dyer AR, Idris-Soven E, Stamler J, Shekelle RB, Schoenberger JA, et al.** Uric acid: a risk factor for coronary heart disease? *Circulation.* 1979;59:969-77.
- 22. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP.** An investigation of coronary heart disease in families. The Framingham Offspring Study. *Am J Epidemiol.* 1979;110:281-90.
- 23. Dawber TR, Meadors GF, Moore FE.** Epidemiologic approaches to heart disease: the Framingham Heart Study. *Am J Public Health.* 1951;41:279-86.
- 24. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med.** 1997; 157:2413-46.
- 25. Crowley LV.** Determination of uric acid. An automated analysis based on a carbonato method. *Clin Chem.* 1964;10:838-44.
- 26. Abell LL, Levy BB, Brodie BB, Kendall FE.** A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity. *J Biol Chem.* 1952;195:357-66.
- 27. Shurtleff D.** Some characteristics related to the incidence of cardiovascular disease and death: Framingham Heart Study 18-year follow-up. In: Kannel WB, Gordon T, eds. The Framingham Study, Section 30. Washington, DC: U.S. Government Printing Office; 1974:17-25.
- 28. Cox DR.** Regression models and life tables (with discussion). *Journal of the Royal Statistical Society.* 1972;34:187-220.
- 29. SAS/STAT Software: Changes and Enhancements through Release 6.11.** Cary, NC: SAS Institute; 1996.
- 30. Wilson PW, Cupples LA, Kannel WB.** Is hyperglycemia associated with cardiovascular disease? The Framingham Study. *Am Heart J.* 1991;121:586-90.
- 31. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL.** Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo study. *JAMA.* 1991;265:627-31.
- 32. Sowers JR.** Diabetes mellitus and cardiovascular disease in women. *Arch Intern Med.* 1998;158:617-21.
- 33. Harris MI, Hadden WC, Knowler WC, Bennett PH.** Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S. population aged 20-74 yr. *Diabetes.* 1987;36:523-34.
- 34. Klein R, Klein BE, Cornoni JC, Maready J, Cassel JC, Tyroler HA.** Serum uric acid. Its relationship to coronary heart disease risk factors and cardiovascular disease, Evans County, Georgia. *Arch Intern Med.* 1973;132:401-10.
- 35. Stetten DW Jr, Heanton JZ.** Intellectual level measured by Army classification battery and serum uric acid concentration. *Science.* 1959;129:1737-9.
- 36. Keil U, Stieber J, Doring A, Chambliss L, Hartel U, Filippiak B, et al.** The cardiovascular risk profile in the study area Augsburg. Results from the first MONICA survey 1984/85. *Acta Med Scand Suppl.* 1988;728:119-28.
- 37. Lewis PJ, Kohner EM, Petrie A, Dollery CT.** Deterioration of glucose tolerance in hypertensive patients on prolonged diuretic treatment. *Lancet.* 1976;1:564-6.
- 38. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. Medical Research Council Working Party on Mild to Moderate Hypertension.** *Lancet.* 1981;2:539-43.
- 39. Murphy MB, Lewis PJ, Kohner E, Schumer B, Dollery CT.** Glucose intolerance in hypertensive patients treated with diuretics: a fourteen-year follow-up. *Lancet.* 1982;2:1293-5.
- 40. Rathmann W, Funkhouser E, Dyer AR, Roseman JM.** Relations of hyperuricemia with the various components of the insulin resistance syndrome in young black and white adults: the CARDIA study. *Coronary Artery Risk Development in Young Adults.* *Ann Epidemiol.* 1998;8:250-61.
- 41. Reaven GM.** Syndrome X: 6 years later. *J Intern Med Suppl.* 1994;736:13-22.
- 42. Messerli FH, Frohlich ED, Dreslinski GR, Suarez DH, Aristimuno GG.** Serum uric acid in essential hypertension: an indicator of renal vascular involvement. *Ann Intern Med.* 1980;93:817-21.
- 43. Quinones Galvan A, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D, et al.** Effect of insulin on uric acid excretion in humans. *Am J Physiol.* 1995;268:E1-5.
- 44. DeFrondo RA, Cooke CR, Andres R, Falloona GR, Davis PJ.** The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man. *J Clin Invest.* 1975;55:845-55.
- 45. Cappuccio FP, Strazzullo P, Farinaro E, Trevisan M.** Uric acid metabolism and tubular sodium handling. Results from a population-based study. *JAMA.* 1993;270:354-9.
- 46. Zweier JL, Kuppusamy P, Lutty GA.** Measurement of endothelial cell free radical generation: evidence for a central mechanism of free radical injury in postischemic tissues. *Proc Natl Acad Sci U S A.* 1988;85:4046-50.
- 47. Ashraf M, Samra ZQ.** Subcellular distribution of xanthine oxidase during cardiac ischemia and reperfusion: an immunocytochemical study. *J Submicrosc Cytol Pathol.* 1993;25:193-201.
- 48. Montor SG, Thoolen MJ, Mackin WM, Timmermans PB.** Effect of azapropazone and allopurinol on myocardial infarct size in rats. *Eur J Pharmacol.* 1987;140:203-7.
- 49. Bolli R.** Oxygen-derived free radicals and postischemic myocardial dysfunction ('stunned myocardium'). *J Am Coll Cardiol.* 1988;12:239-49.
- 50. Friedl HP, Smith DJ, Till GO, Thomson PD, Louis DS, Ward PA.** Ischemia-reperfusion in humans. Appearance of xanthine oxidase activity. *Am J Pathol.* 1990;136:491-5.
- 51. Huizer T, de Jong JW, Nelson JA, Czarnecki W, Serruys PW, Bonnier JJ, et al.** Urate production by human heart. *J Mol Cell Cardiol.* 1989;21: 691-5.
- 52. Lazzarino G, Raatikainen P, Nuutilainen M, Nissinen J, Tavazzi B, Di Pierro D, et al.** Myocardial release of malondialdehyde and purine compounds during coronary bypass surgery. *Circulation.* 1994;90:291-7.
- 53. Sahebjani H.** Changes in urinary uric acid excretion in obstructive sleep apnea before and after therapy with nasal continuous positive airway pressure. *Chest.* 1998;113:1604-8.
- 54. Hayabuchi Y, Matsuoaka S, Akita H, Kuroda Y.** Hyperuricemia in cyanotic congenital heart disease. *Eur J Pediatr.* 1993;152:873-6.
- 55. Porter KB, O'Brien WF, Benoit R.** Comparison of cord purine metabolites to maternal and neonatal variables of hypoxia. *Obstet Gynecol.* 1992;79: 394-7.
- 56. Saugstad OD.** Hypoxanthine as a measurement of hypoxia. *Pediatr Res.* 1975;9:158-61.
- 57. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB.** Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97:1837-47.